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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/638,267	08/14/2000	Vincent P. Stanton JR.		9607

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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/638,267	STANTON, VINCENT P.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Ocotber 17, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *122 and 123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *122 and 123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 12, 2003 and October 17, 2003. Currently, claims 122-123 are pending.

Priority

2. This application claims priority to several US applications including 09/596,033, filed June 15, 2000. Upon review of 09/357,743, the specification fails to disclose each of the mutations of the instant claims. For example, the specification fails to teach 464, 519, and 1784. Therefore, the instant claims appear to receive the benefit of June 15, 2000.

Drawings

3. The drawings are acceptable.

Specification

4. The attempt to incorporate subject matter into this application by reference to Genbank Accession Number U09806 is improper because the specification does not specifically incorporate a particular Genbank Sequence by specific reference. The MPEP states that "Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). See MPEP § 608.01(p)."

5. The amendments filed June 20, 2002 and October 22, 2003 are objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows. The amendments attempt to incorporate GenBank Accession Number U09806 for the methylenetetrahydrofolate reductase cDNA sequence. It is readily apparent that there is more than one version the Genbank Accession Number presented over time. The declaration filed October 22, 2003 attempts to amend the sequence GI:6174884 to an earlier GI:945022. The instant specification does not specifically teach which GI number was used in the instant specification. It is clear that there were at least three modifications to this Genbank Accession Number U09806 prior to the instant filing date of August 14, 2000 and the specification does not clearly indicate which sequence was relied upon in the application. To bring in any one of the three sequences would constitute new matter because the specification fails to indicate which accession number was being relied upon by the instant specification.

A review of the instant specification further supports this concept of new matter. On page 120, the specification teaches that Methylenetetrahydrofolate Reductase (U09806) has several mutations including 677C or T which causes Ala223Val. On page 190-191, the specification teaches that U09806 Human methylenetetrahydrofolate reductase mRNA has a mutation at 668 C to T which causes A223V. The amino acid variant is identical, however the nucleic acid position within U09806 is different. Thus, the specification appears to contain two different numbering systems for the same

Genbank Number. It is unclear which numbering system is correct and whether the systems are for different versions of the Genbank Number. Since the specification does not identify any of the Genbank Numbers by either date or GI number, it is new matter to bring in either of the sequences.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Matter

6. Claims 122-123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendments attempt to incorporate GenBank Accession Number U09806 for the methylenetetrahydrofolate reductase cDNA sequence. It is readily apparent that there is more than one version the Genbank Accession Number presented over time. The declaration filed October 22, 2003 attempts to amend the sequence GI:6174884 to an earlier GI:945022. The instant specification does not specifically teach which GI number was used in the instant specification. It is clear that there were at least three modifications to this Genbank Accession Number U09806 prior to the instant filing date of August 14, 2000 and the specification does not clearly indicate which sequence was relied upon in the application. To bring in any one of the three sequences would constitute new matter because the specification fails to indicate which accession number was being relied upon by the instant specification.

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Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 122-123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 122-123 are drawn to a method for selecting a treatment for a patient suffering from a condition or disease by assaying for one of the 5 specifically recited mutations wherein the presence of the variation in the MTHFR gene is indicative of the effectiveness of the treatment for the condition. The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification.

The specification provides teaches that the MTHFR gene has variations which modulate 5-FU/FA Pharmacology. Table 3, page 119-120, teaches that mutations at 129, 677, 1068, 1298 and 308 are associated variations which modulate 5-FU/FA Pharmacology. It is noted that none of these mutations are within the instant claims. Thus, this fails to support the enablement for the instant claims.

Each of the mutations in the specification are within the human MTHFR sequences. There is no teachings in the specification with respect to any patient. Patient may broadly encompass humans, mice, rats, dogs, for example. Thus, the instant specification provides no guidance to each of these additional mammals.

Of the five variations within the instant claims, only one of the variations changes the amino acid sequence. The mutation at 464 causes M155R (Table 10). Mutations which do not change the amino acid sequence may not affect the encoded protein in any significant manner. It is unpredictable that silent mutations change the function of the protein such that effectiveness of treatments is altered. Table 3 specifically states that the amino acid changes affect MTHFR activity. Thus, it is unclear and unpredictable whether the silent mutations have any affect on the activity or alter the effectiveness of treatment of a condition or disease.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Working Examples

The specification has no working examples of associating the disclosed polymorphisms with a method of selecting a treatment for a patient suffering from a condition or disease and the effectiveness of the treatment.

The unpredictability of the art and the state of the prior art

The post filing date art teaches that there is a level of unpredictability in associating particular MTHFR mutations with effectiveness of treatments for diseases or conditions. The post filing date art teaches that not each of the mutations within the

MTHFR gene have the same diagnostic or effectiveness for treatment as each other mutation, thus supporting the idea that each of the mutations within a single gene do not act in concert with each other. Specifically, Perentesis et al. (Blood, Vol. 102, No. 11, pages 139a, November 2003) teaches that polymorphisms in MTHFR at nucleotides 677 and 1298 which lead to amino acid substitutions and reduction in enzyme activity were studied. Perentesis teaches that in children with Down syndrome and AML receiving chemotherapy, the risk of death was increased almost 7-fold in those with at least one low activity MTHFR allele. Further MTHFR genotype C677T had no impact on treatment outcome in either group of children. These data show that MTHFR 1298 genotype influences outcome of therapy in children with Down syndrome and AML, but not in those with AML without Down syndrome. Thus, Perentesis teaches that each polymorphism has a different effect on the effectiveness of a treatment. Further, it is clear that each polymorphism must be analyzed separately for each therapy for a particular condition, as patients with Down syndrome and MAL were affected, but not those with AML alone.

Sohn et al. (J. of National Cancer Institute, Vol. 96, No. 2, pages 134-144, January 2004) teaches that different treatments are affected differently by the same mutation. Sohn specifically teaches that functional evidence regarding the relevance of polymorphisms is currently lacking. The MTHFR 677T mutation increased chemosensitivity of colon and breast cancer to 5FU, but decreased chemosensitivity of breast cancer cells to MTX. Sohn cautiously states that the MTHFR C677T polymorphism may be a useful pharmacogenetic determinant for providing rational and effective tailored chemotherapy (abstract). Sohn teaches that currently available clinical studies do not provide conclusive evidence that SNPs have functional consequences and in the absence of such data, the pharmacogenetic relevance of the SNPs remains

generally uncertain (page 140, col. 2). Sohn teaches that currently available clinical studies do not provide conclusive evidence that SNPs have functional consequences and in the absence of such data, the pharmacogenetic relevance of the SNPs remains generally uncertain. Sohn specifically states that although these results were observed, there is a need to confirm them in human studies (page 142). The differences do not reach statistical significance, likely because of the small sample size. Thus, large clinical trials are therefore necessary to confirm the effect of the MTHFR C677T polymorphism on treatment response and survival in cancer patients receiving chemotherapy.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied and analyzed to practice the claimed invention as broadly as claimed. The post filing date art clearly teaches that each mutation in the MTHFR does not react similarly to different treatments for diseases or conditions, as exemplified by the fact that C677T and A1298C have different impacts on treatment outcome in the children analyzed. Thus, the skilled artisan would be required to individually examine each variation with respect to each treatment for each disease or condition. The skilled artisan would not be able to make any reliable prediction of the effectiveness of one treatments based upon the information gained from another mutation. The instant specification does not appear to analyzed any mutation for any effectiveness of a treatment for a disease or condition. Thus, the skilled artisan would be required to perform additional undue and unpredictable assays to determine whether a mutation is associated with the effectiveness of said treatment with a condition or disease.

Moreover, the post filing date art makes it clear that different treatments have different effectiveness with respect to a particular polymorphism. The prior art teaches that the C677T polymorphism causes increased sensitivity to 5FU, but decreased chemosensitivity to MTX. Thus, the skilled artisan would be required to test and experiment with each particular treatment of interest because polymorphisms do not act similarly for each treatment. Thus, there would be not reasonable expectation of success that if one particular treatment was effective in the presence of a mutation that all treatments would be effective in the presence of a mutation since the art clearly teaches that 5Fu increases chemosensitivity whereas MTX decreases chemosensitivity. Therefore, it would be unpredictable whether a particular treatment would be effect for each polymorphisms absent undue and unpredictable experimentation.

While one could conduct additional experimentation to determine whether each polymorphism required by the instant claims was effective for a treatment for a disease or condition, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. It is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where there is no association provided between each polymorphism and treatments for conditions and disease. Further, the art and the specification provides insufficient guidance to overcome the art recognized problems associated with the association between the polymorphisms and the effectiveness of a treatment. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 122-123 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The claims are drawn to a method for selecting a treatment for a patient from a condition or disease by determining whether cells of the patient contain a variance in MTHFR wherein the presence or absence of the variance is indicative of the effectiveness of the treatment for the condition or disease. There is no selection step in

this method. Thus, it is unclear how the ordinary artisan would make a selection for treatment of a patient based upon the claimed method.

Conclusion

9. No claims allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
September 30, 2004